DETAILED ACTION

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Andriae M. Holt.

Claims 20-31 and 33-40 are pending in the application. The examiner notes Applicant's request for enrollment in the First Action Interview Pilot has been withdrawn due to Applicant's traversal of the Restriction Requirement mailed on March 31, 2010.

Election/Restrictions

Applicant's election with traverse of Group I, claims 20-34 in the reply filed on April 30, 2010 is acknowledged. The traversal is on the ground(s) that as stated in the Declaration of Carolyn Westhoff, MD, one would not have expected estetrol to be pharmacologically useful due to the anticipated low elimination half-life and the known low binding affinity. Applicant also argues that one skilled in the art would not have expected estetrol, the special technical feature, to be pharmacologically useful, and one would not have expected it to have such a long elimination half-life. This is not found persuasive because the prior art reference, Pike et al., specifically discloses that estetrol is used for the treatment of benign gynecological disorders. By the mere fact that estetrol is listed as one of the estrogen derivatives that can be used to treat benign gynecological disorders, the skilled artisan would have expected estetrol to be pharmacologically useful. The fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte*

Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In addition, as provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The additional arguments discussed in the Declaration filed March 30, 2010 will be addressed further in the Office Action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-31 and 33-40 are pending in this application. Claims 35-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 30, 2010.

Claims 20-31 and 33-34 will presently be examined to the extent they read on the elected subject matter of record

Priority

This application is a national stage entry for PCT/NL03/00718 filed October 23, 2003 which claims benefit to Foreign European Patent Application 02079414.5 filed October 23, 2002.

Information Disclosure Statement

Receipt of Information Disclosure Statements filed November 6, 2006 and January 11, 2010 is acknowledged.

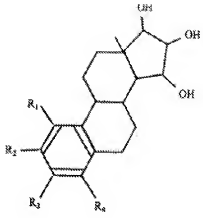
Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-28 and 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-32 and 45-54 of copending Application No. 10/521,040 ('040). Although the conflicting claims are not identical, they are not patentably distinct from each other because each is drawn to a method of treating estrogen-suppressed tumors in a mammal comprising the administration of a therapeutically effective amount of an estrogenic component to said mammal, said estrogenic component being selected from the group consisting of



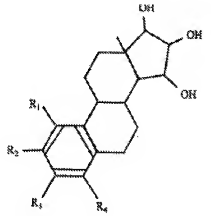
substances represented by the following formula . The instant application does not recite the tumors are selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, endometriosis, and uterine fibroid as in co-pending Application '040. However, it would have been obvious to one of ordinary skill in the art to try the same estrogenic compound as recited in the claims of the instant application to treat the specific tumors recited in co-pending application '040 because the estrogenic compound is useful for treating estrogen related benign and malign tumors as suggested by the instant claims. The tumors recited in co-pending application '040 are a subset of benign and malign tumors as recited in the instant claims. For these reasons, one of ordinary skill in the art would conclude that the invention defined in the instant claims would have been an obvious variation of the invention defined in the claims of copending application '040.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-31 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating estrogen-suppressed tumors in a mammal, said method comprising the administration of a therapeutically effective amount of an estrogenic component to said mammal, said estrogenic component being selected from the group consisting of substances represented by the formula 

, does not reasonably provide enablement for a method for the ***prevention*** of estrogen-suppressed tumors in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without an undue amount of experimentation.

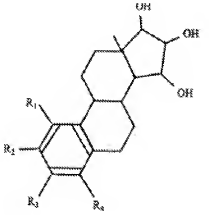
Applicant has not provided a special definition for the term "preventing", therefore, the examiner is using the definition as defined in The Merriam-Webster Online Dictionary. The Merriam-Webster Online Dictionary defines prevention as "to keep from happening or existing". Using the common definition of preventing,

applicant's specification fails to provide enough detailed teachings for an artisan to make and use the invention commensurate within the scope of the claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, one of ordinary skill in the art could not practice the invention without undue experimentation.

1) Scope or breadth of the claims

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, a method for treating estrogen-suppressed tumors in a mammal, said method comprising the administration of a therapeutically effective amount of an estrogenic component to said mammal, said estrogenic component being selected from the group consisting of substances represented by the

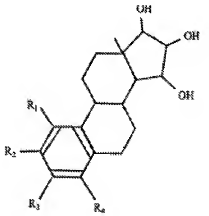


formula .

However, Applicant is purporting to have a method useful for the prevention of estrogen-suppressed tumors.

2) Nature of the invention

The nature of the invention is directed to a method for treating estrogen-suppressed tumors in a mammal, said method comprising the administration of a therapeutically effective amount of an estrogenic component to said mammal, said estrogenic component being selected from the group consisting of substances



represented by the formula .

3) Relative level of skill possessed by one of ordinary skill in the art

The relative level of skill possessed by one of ordinary skill in the art of medical research is relatively high, as a majority of lead investigators directing scientific research and development in this particular technological area possess an Ph.D. in a scientific discipline such as organic synthetic chemistry, polymer chemistry, medicinal chemistry, biochemistry, pharmacology, biology or the like.

4) State of, or the amount of knowledge in, the prior art

It is known in the current state of the art that tumors arise from many different aspects and causes, such as diet, environment and genetics. According to the Colon Cancer Publication, cancer is the transformation of normal cells. Most colon cancers are adenocarcinomas-tumors that develop from the glands lining the colon's inner wall. These tumors are sometimes referred to as colorectal cancer, reflecting the fact that the rectum, the end portion of the colon, can also be affected (Colon Cancer Overview, page 2). The Colon Cancer Publication teaches that people with any of several conditions known as adenomatous polyposis syndromes have a greater-than-normal risk for colorectal cancer. In these conditions, numerous adenomatous polyps develop in the colon, ultimately leading to colon cancer. Adenomatous polyposis syndromes tend to run in families (page 2, Colon Cancer Causes). The Colon Cancer Publication teaches that another group of colon cancer syndromes, termed hereditary nonpolyposis colorectal cancer (HNPCC) syndromes, also run in families. In these, syndromes, colon cancer develops without the precursor polyps. HNPCC syndromes are associated with a genetic abnormality. HNPCCC syndromes are sometimes linked to tumors in other parts of the body (page 2, Colon Cancer Causes). Therefore, as indicated by the

teachings of The Colon Cancer Publication, those colon cancers that are hereditary are not preventable.

5) Level or degree of predictability, or a lack thereof, in the art

The Examiner has provided evidence in the state of and knowledge in the art showing that some forms of colon cancer are not preventable because theses diseases are inherited and therefore, unpreventable.

The skilled artisan would view that prevention of estrogen-suppressed tumors is highly unpredictable.

6) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to preventing estrogen-suppressed tumors. Applicant discloses three examples in the specification, see pages 14-19. The results in example 1 indicate that in groups of animals treated with an increasing dose range of estetrol, the number of malignant tumors declines as a function on increasing the daily oral dose of estetrol. Example 2 provides results of steroid binding assays. The results in example 3 indicate that estetrol (E4) suppressed mammary tumor development; however, it did not prevent tumor development.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

One of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately determine whether said estrogenic

compound when administered to a mammal in the corresponding instant method does in fact prevent the occurrence of estrogen-suppressed tumors.

Therefore, in conclusion, it is readily apparent from the aforementioned disclosure, in conjunction with a corresponding lack of scientific data and working embodiments, the prevention of estrogen-suppressed tumors is not enabled because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-31 and 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recites that said estrogen component selected from the group consisting of "precursors" capable of liberating a substance according to the aforementioned formula "when used in the present method".

Since the term "precursor" is not defined by the specification, and the specification does not provide a standard for ascertaining the requisite degree;

therefore, one of ordinary skill in the art would not be reasonably apprised the intended limitation for the "precursor" in such a manner that whether the precursor is capable of liberating the estrogenic component only when used in the present method or it is also capable of liberating the estrogenic component when used in other methods. Applicant is advised to remove the term "when used in the present method" recited in instant claim 25.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

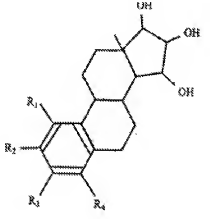
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-23, 25-30 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kragie et al. (WO 02/30355) in view of the Estrogens in the Treatment of Advanced Prostate Cancer Publication (1995) and Spicer et al. (US 5,340,584).

Applicant's Invention

Applicant claims a method for treating estrogen-suppressed tumors in a mammal, said method comprising the administration of a therapeutically effective amount of an estrogenic component to said mammal, said estrogenic component being selected from the group consisting of substances represented by the



formula .

Determination of the scope of the content of the prior art (MPEP 2141.01)

Kragie et al. teach a composition comprising estrogen function replacement (EFR) agent(s) that can replace the role of estrogens, such as estradiol, in the functions of humans and animals. These compositions can be administered to humans or animals under the influence of compounds, devices and/or biologics that can inhibit the activity of their aromatase enzyme, estrogen synthetase (page 4, lines 29-36). Kragie et al. further teach a method of using compositions containing EFR agents, to treat humans or animals when they are under the influence of compounds, devices and/or biologics that can inhibit the activity of their aromatase enzymes. The method comprises

administering EFR agent(s) through oral, inhaled, topical, parenteral, rectal, intravaginal, intraurethra, intrathecal or implanted route(s) in combination with the exposure to aromatase inhibitor(s). The EFR agent(s) can be administered simultaneously or disjoint in time, preceding or succeeding the administration of the aromatase inhibitor. The EFR agent(s) can be given for more, less or the same duration as the aromatase inhibitor agent(s) (page 5, lines 4-12). Kragie et al. teach that specific examples of the invention include, but are not restricted to, combining EFR agents with the intentional (therapeutic) and/or nonintentional exposure to aromatase inhibitors in humans and other animals, chemotherapies given for breast cancer and for prostate cancer (page 5, lines 19-22, line 32).

Kragie et al. teach that estrogens are a class of gonadal steroid hormones associated with the development and maintenance of secondary female sex characteristics, control of the cyclical changes in the reproductive cycle, are required for pregnancy maintenance and have an anabolic effect on protein metabolism and water retention. An EFR agent is defined as one that can selectively, partially, or totally replace the functions of the estrogen compounds, such as estradiol and estrone that are synthesized from the substrates of the estrogen synthetase/aromatase enzyme, in a human or other animal (page 8, lines 6-19). Kragie et al. teach an example of EFR agents includes estetrol (page 10, lines 3-5). Kragie et al. teach the EFR agent(s) component would be dosed to provide sufficient biological activity for the desired estrogen function at the tissue target while in the presence of, or subsequent to exposure to, the aromatase inhibitor. The EFR agent(s) component may be

administered with the intent to provide biological availability at the tissue target at a local concentration that would, minimally, meet the EC50 value (half-maximal efficacy concentration) for the desired estrogenic function, as determined from an examination of dose-response (page 11, lines 30-35-page 12, lines 1-4). Kragie et al. teach that any biologically-acceptable oral dosage form well known to persons of ordinary skill in the art, and any combinations thereof, can be considered for use (page 12, lines 30-35). Kragie et al. teach aromatase inhibitors are used to diminish the production of estrogens at the site of cancerous or hyperplastic prostate tissue. These agents are usually given systemically and the production of estrogen is reduced throughout the body. Selective EFR agents could be added to the therapy to reduce the effects of estrogen-depletion on bone resorption and cardiovascular disease, without stimulating prostate cancer cells (page 22, lines 23-28).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kragie et al. do not specifically disclose examples of the use of the claimed compound, estetrol, in a method of treating estrogen-suppressed tumors in a mammal or the method comprises co-administration of a progestogen. It is for this reason The Estrogens in the Treatment of Advanced Prostate Cancer Publication and Spicer et al. are joined as secondary references.

The Estrogens in the Treatment of Advanced Prostate Cancer Publication teaches that the administration of estrogens to a man has a series of complex effects on that man's hormonal system (page 1, Introduction). The Estrogens in the Treatment of

Advanced Prostate Cancer Publication teaches that worldwide, DES, diethylstilbestrol, is still one of the most commonly used agents for the hormonal treatment of advanced prostate cancer for one reason if not other. It is very low in price. The critical disadvantage is that it has been associated with a relatively high risk for cardiovascular side effects at higher dosages.

Spicer et al. teach a method to treat and to reduce the risk of breast cancer, ovarian cancer, and endometrial cell proliferation (column 14, line 11-12, line 30, Table 1 and line 38-41) comprising administering an effective amount of an estrogen composition, such as estetrol, in a mammal for a period of about 2 months to about six months (column 20, claims 31-32). Spicer et al. teach that while estrogen has significant positive effects in conjunction with the use of a GnRH composition, it is nonetheless important to recognize the potential risks inherent in such treatment (col. 12, lines 64-68). Spicer et al. teach that add back therapy with low-dose estrogen and progestogen is required to prevent harmful hypoestrogenic effects and to protect the endometrium (col. 13, lines 7-10).

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kragie et al., The Estrogens in the Treatment of Advanced Prostate Cancer Publication, and Spicer et al. and use of the claimed compound, estetrol, in a method of treating estrogen-suppressed tumors in a mammal. One skilled in the art at the time the invention was made would have been motivated to try the

estetrol in the treatment of prostate cancer because Kragie et al. specifically teach that EFR agents are combined with the intentional (therapeutic) and/or nonintentional exposure to aromatase inhibitors in humans and other animals, as chemotherapies given for breast cancer and prostate cancer. One skilled in the art at the time the invention was made would have been further motivated to try the estetrol in the treatment of an estrogen-suppressed tumor, such as prostate. Kragie et al. further teach an EFR agent, such as estetrol, is defined as one that can selectively, partially, or totally replace the functions of the estrogen compounds. The Estrogens in the Treatment of Advanced Prostate Cancer Publication teaches that estrogens are widely used to treat prostate cancer, however, there are risks. As such, the skilled artisan would have been motivated to try estetrol, an EFR agent, because EFR agents could be added to the therapy to reduce the effects of estrogen-depletion on bone resorption and cardiovascular disease, without stimulating prostate cancer cells.

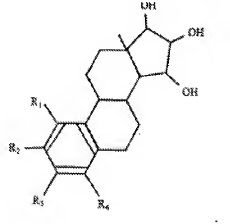
It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kragie et al., The Estrogens in the Treatment of Advanced Prostate Cancer Publication, and Spicer et al. and use of the claimed compound, estetrol, wherein the method comprises co-administration of a progestogen. Kragie et al. specifically teach that EFR agents are combined with the intentional (therapeutic) and/or nonintentional exposure to aromatase inhibitors in humans and other animals, as chemotherapies given for breast cancer and prostate cancer. One skilled in the art at the time the invention was made would have been motivated to add progestogen to the compositions for the treatment of prostate cancer because Spicer et al. teach that add

back therapy with low-dose estrogen, which can be estetrol, and progestogen is required to prevent harmful hypoestrogenic effects. As such, the skilled artisan would have been motivated to add progestogen to the formulation with a reasonable expectation of success.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited references.

Claims 20-23, 26, 29-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kragie et al. (WO 02/30355) in view of al-Azzawi Abstract (2002).

Applicant's Invention

Applicant claims a method for treating estrogen-suppressed tumors in a mammal, said method comprising the administration of a therapeutically effective amount of an estrogenic component to said mammal, said estrogenic component being selected from the group consisting of substances represented by the formula 

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Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Kragie et al. with respect to the 35 U.S.C. 103(a) rejection is hereby incorporated and are therefore applied in the instant rejection as discussed above.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kragie et al. do not specifically disclose examples of the use of the claimed compound, estetrol, in a method of treating colorectal tumors. It is for this reason the al-Azzawi Publication (al-Azzawi) is joined as a secondary reference.

Al-Azzawi teaches that carcinoma of the colon is common and its incidence varies according to the geographical location and dietary habits. Al-Azzawi teaches that estrogen use confers overall protection, with a reduction in the incidence of colon adenoma and carcinoma of about 30%. Estrogen use reduces the colon cancer-related mortality. The risk of colon cancer is decreased among current and recent users of postmenopausal HRT, but the molecular mechanisms involved remain unclear (entire Abstract).

Finding a prima facie obviousness Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kragie et al., and the al-Azzawi Publication and use of the claimed compound, estetrol, in a method of treating estrogen-suppressed tumors, colorectal tumors, in a mammal. One skilled in the art at the time the invention was

made would have been motivated to try the estetrol in the treatment of a colorectal tumor because Kragie et al. specifically teach that EFR agents are combined with the intentional (therapeutic) and/or nonintentional exposure to aromatase inhibitors in humans and other animals, as chemotherapies given for breast cancer and prostate cancer. One skilled in the art at the time the invention was made would have been further motivated to try the estetrol in the treatment of an estrogen-suppressed tumor, such as colorectal, because Kragie et al. teach an EFR agent, such as estetrol, is defined as one that can selectively, partially, or totally replace the functions of the estrogen compounds. The al-Azzawi Publication teaches that estrogens are widely used to treat colon cancer. As such, the skilled artisan would have been motivated to try estetrol, an EFR agent, because EFR agents could be added to the therapy to reduce the effects of estrogen-depletion on bone resorption and cardiovascular disease, without stimulating cancer cells.

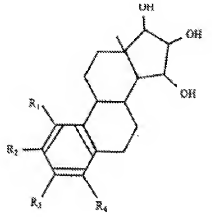
Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited references.

Claims 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kragie et al. (WO 02/30355) in view of the Younglai Publication (1968).

Applicant's Invention

Applicant claims a method for treating estrogen-suppressed tumors in a mammal, said method comprising the administration of a therapeutically effective

amount of an estrogenic component to said mammal, said estrogenic component being selected from the group consisting of substances represented by the

formula 

. Applicant claims that precursors capable of liberating a substance can be used in the method of treating estrogen-suppressed tumors.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Kragie et al. with respect to the 35 U.S.C. 103(a) rejection is hereby incorporated and are therefore applied in the instant rejection as discussed above.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kragie et al. do not specifically disclose that precursors of the formula claimed capable of liberating a substance can be used in the method of treating estrogen-suppressed tumors. It is for this reason the Younglai Publication (Younglai) is joined as a secondary reference.

Younglai teaches that following the intravenous administration of labeled C18-

steroids to subjects in the third trimester of pregnancy, labeled estetrol was isolated form the glucosiduronate fraction of the urine. In order to determine the precursor role of neutral steroids in the formation of estetrol and 15α-hydroxyestradiol, the following pairs of substrates were injected into subjects in the third trimester of pregnancy; (7-3H)-16α-hydroxydehydroisoandrosterone sulfate and (4-14C)-dehydroisoandrosterone sulfate. Younglai teaches that after purification, the estetrol was identified by infrared analysis and melting point. All the substrates studied were converted to urinary estetrol, and from the 3H/14C ratios and percentage conversions it was apparent that dehydroisoandrosterone sulfate was the best precursor. It was also possible to conclude that 15α-hydroxyandrostenedione was a better precursor than 16α-hydroxyandrostenedione in the formation of urinary estetrol.

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kragie et al., and the Younglai Publication and use precursors of the formula claimed capable of liberating a substance in the method of treating estrogen-suppressed tumors. Kragie et al. teach that estetrol is used in the treatment of breast and prostate cancer. One skilled in the art at the time the invention was made would have been motivated to try the precursors of estetrol in the treatment of a estrogen-suppressed tumors because Younglai teaches that the claimed precursors were effectively converted to urinary estetrol. As such, the skilled artisan would have been motivated to try the precursors in the method of treating estrogen-suppressed

tumors as a matter of routine experimentation and optimization to find inexpensive compounds that are known to convert to estetrol.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited references.

Response to Declaration

The declaration under 37 CFR 1.132 filed March 30, 2010 is insufficient to overcome the restriction requirement as set forth in the last Office action because: Applicant's opinion that prior to October 23, 2002 a person of ordinary skill in the art would not have expected estetrol to be pharmacologically useable has not been found convincing. Hence, the declaration is nothing more than an opinion affidavit, which is accorded little weight. MPEP 716.01(c) teaches the following in reference to opinion evidence:

> Although an affidavit or declaration which states only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application. *In re Brandstadter*, 484 F.2d 1395, 179 USPQ 286 (CCPA 1973).

Applicant argues that it is the opinion of Dr. Westhoff that prior to October 23, 2002, a person of ordinary skill in the art would not have expected that estetrol can be used to treat estrogen-suppressed tumors, such as colorectal tumors or prostate tumors or would not have expected estetrol to be pharmacologically active when orally administered. This is not found persuasive because the prior art reference, Pike et al., specifically discloses that estetrol is used for the treatment of benign gynecological disorders. By the mere fact that estetrol is listed as one of the estrogen derivatives that

can be used to treat benign gynecological disorders, the skilled artisan would have expected estetrol to be pharmacologically useful. The fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In addition, Applicant provides arguments against cited references in co-pending applications, many of which have not been used in the instant Office Action. As such, the declaration cannot be used to overcome the obviousness rejections of the instant application.

None of the claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is (571)272-9328. The examiner can normally be reached on 7:00 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richter Johann can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/John Pak/
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